Lasers in Surgery and Medicine 26:201–207 (2000)

Prophylactic Fluconazole Promotes Reepithelialization in Full-Face Carbon Dioxide Laser Skin Resurfacing

Howard Conn, MD,[1,2]* and Vandana S. Nanda, MD[1,3]

[1]Beckman Laser Institute and Medical Clinic, Irvine, California 92612
[2]Department of Ophthalmology, University of California, Irvine, Irvine, California 92862
[3]Department of Dermatology, University of California, Irvine, Irvine, California 92868

Background and Objective: **Laser skin resurfacing is used to treat photodamaged skin, rhytids, and acne scarring. Many patients are placed on antibiotics and antivirals pre- and postoperatively. The purpose of this study was to determine whether prophylactic fluconazole increased the rate of reepithelialization in patients undergoing full-face CO_2 laser skin resurfacing.**
Study Design/Materials and Methods: **Ninety-one patients underwent full-face CO_2 laser skin resurfacing with the Coherent Ultrapulse 5000C. At least two passes of 300 mJ, density 5, were used except periocularly. Study group I consisted of 48 consecutive patients who received either cephalexin or ciprofloxacin for 7 days postoperatively. Study group II consisted of 43 patients who received 300 mg of fluconazole on postoperative days 3–8, in addition to ciprofloxacin. Both groups received acyclovir 400 mg t.i.d. pre- and postoperatively.**
Results: **Time to complete reepithelialization was compared between the groups by t-test. Group II reepithelialized significantly faster than group I (7.65 ± 1.20 days vs. 10.27 ± 2.94 days; $P < 0.0001$). Ninety-five percent of patients receiving fluconazole (group II) healed completely by day 9 versus only 53% of patients in group I.**
Conclusion: **Fluconazole administered postoperatively between days 3 and 8 significantly promotes reepithelialization in patients undergoing full-face CO_2 laser skin resurfacing. Lasers Surg. Med. 26:201–207, 2000.**

Key words: CO_2 laser; prophylaxis; antifungal; wound healing

INTRODUCTION

Laser skin resurfacing is a well-accepted treatment for actinically damaged skin, rhytides, and acne scarring. Pulsed carbon dioxide (CO_2) laser resurfacing of photoaged facial skin has become extremely popular. Impressive cosmetic results can be obtained and complications minimized with proper operative techniques, instrumentation, and peri- and postoperative wound management [1]. Noninfectious complications include prolonged erythema, pigmentary changes, textural changes, acne and milia formation, hypertrophic scarring, and ectropion formation [2–4]. Postoperative infectious complications are most commonly caused by bacteria, herpes simplex virus, or *Candida* species. An overall incidence of 8.1% of culture-proven infections in full-face resurfacing has been documented [5]. Gram-negative bacteria were the most common pathogens (41%), followed by Gram-positive bacteria (*Staphylococcus aureus*, 35%; *Staphylococcus epidermidis*, 35%), *Candida* species (24%), and herpes simplex virus (5.9%) [5]. Infection with multiple organisms has been noted in 50% of patients [5,6]. Complaints of increasing or persis-

*Correspondence to: Howard Conn, MD, Beckman Laser Institute, 1002 Health Sciences Road East, Irvine, CA 92612. E-mail: hconn@laser.bli.uci.edu

Accepted 22 September 1999

TABLE 1. Antibacterial and Antifungal Regimens of Study Groups

Group I	48 study patients received either cephalexin 250 mg. q.i.d. or ciprofloxin 500 mg. b.i.d. from the day of surgery to 7 days postoperatively; herpes prophylaxis with acyclovir 400 mg three times daily starting 3 days before surgery and continuing for 8 days postoperatively
Group II	43 study patients receiving ciprofloxacin 500 mg b.i.d. on the day of surgery to 7 days postoperatively; in addition, 300 mg. of fluconazole was also given daily for 5 days on postoperative days 3–8; herpes prophylaxis with acyclovir 400 mg three times daily starting 3 days before surgery and continuing for 8 days postoperatively

tent pain, burning, itching, and retarded healing should trigger suspicion of brewing infection [2,4,7].

In our patients undergoing full-face CO_2 laser skin resurfacing, we observed areas of increased crusting, yellowish exudate, and tendency toward incomplete and retarded healing beginning at postoperative day 3. Because our patients were being prophylactically treated with antibiotic and antiviral medications, we suspected *Candida* colonization as the most likely cause of wound-healing delay. Therefore, we decided to study the effect of proplylactic treatment with systemic fluconazole in patients undergoing full-face laser skin resurfacing.

TABLE 2. Basic Preoperative and Postoperative Regimen

Preoperative
Herpes prophylaxis with acyclovir 400 mg three times daily starting 3 days before surgery and continuing for 8 days postoperatively
Face, hair and hands cleaned with chlorhexidine (e.g., Hibiclens) for 1 day before the procedure
Immediate preoperative cleaning of the face with Septisol (Calgon Vestal Laboratories, St. Louis, MO) and thorough rinsing with normal saline
Postoperative
Application of Aquaphor Healing Ointment and N-terface, a bio-occlusive dressing, for 1 day immediately after the procedure
Frequent soaking of the treated area with 2% acetic acid solution until epithelialization was complete
Frequent hand washing with chlorhexidine for 7 days postoperatively; all other topical medications and cosmetics were withheld until complete reepithelialization occurred

MATERIALS AND METHODS

This study includes data from 91 consecutive patients who underwent CO_2 laser skin resurfacing of the full face between October 7, 1996 and August 6, 1998. The Ultrapulse 5000C (Coherent Medical Inc., Palo Alto, CA) carbon dioxide laser was used in all patients. Details of the technique have been published previously [1]. With the computerized pattern generator, at least two passes of 300 mJ, density 5, were used over all areas on the face, except periocularly. The lower eyelid skin and lateral canthus regions were treated with one pass of 250 mJ, density 4 and, in some cases, a second pass of 200 mJ, density 4. The upper eyelid skin was treated with one pass of 200 mJ, density 4. Two-thirds of the patients underwent concurrent eyelid surgery, including transcutaneous upper lid and transconjunctival blepharoplasty and bilateral lateral canthal suspension. Tables 1 and 2 list the design of the two study groups and the basic pre- and postoperative regimens.

RESULTS

Ninety-one patients underwent full-face CO_2 laser resurfacing. Time to complete reepithelialization was compared between study groups I (48 patients) and II (43 patients) by *t*-test. Study group II (patients receiving fluconazole and ciprofloxacin) reepithelialized significantly faster than those who did not receive fluconazole (7.65 ± 1.2 days vs. 10.27 ± 2.94 days). $P < 0.0001$ was considered statistically significant. Ninety-five percent of patients treated with systemic fluconazole therapy (group II) healed by postoperative day 9 versus only 53% of those patients using only antibiotic and antiviral medications (study group I; Fig. 1). Patients receiving fluconazole were much less likely to develop crusting, yellowish exudate, and failure to heal equally in all areas (Figs. 2–3). These patients expressed increased satisfaction with the procedure because they were able to resume more quickly their daily activities and work.

DISCUSSION

The purpose of this study was to observe the effects of prophylactic fluconazole in patients undergoing full-face laser resurfacing. In our office we noted delayed wound healing, crusting, and yellowish exudate between days 3 and 8 postoperatively. Infections similarly were present

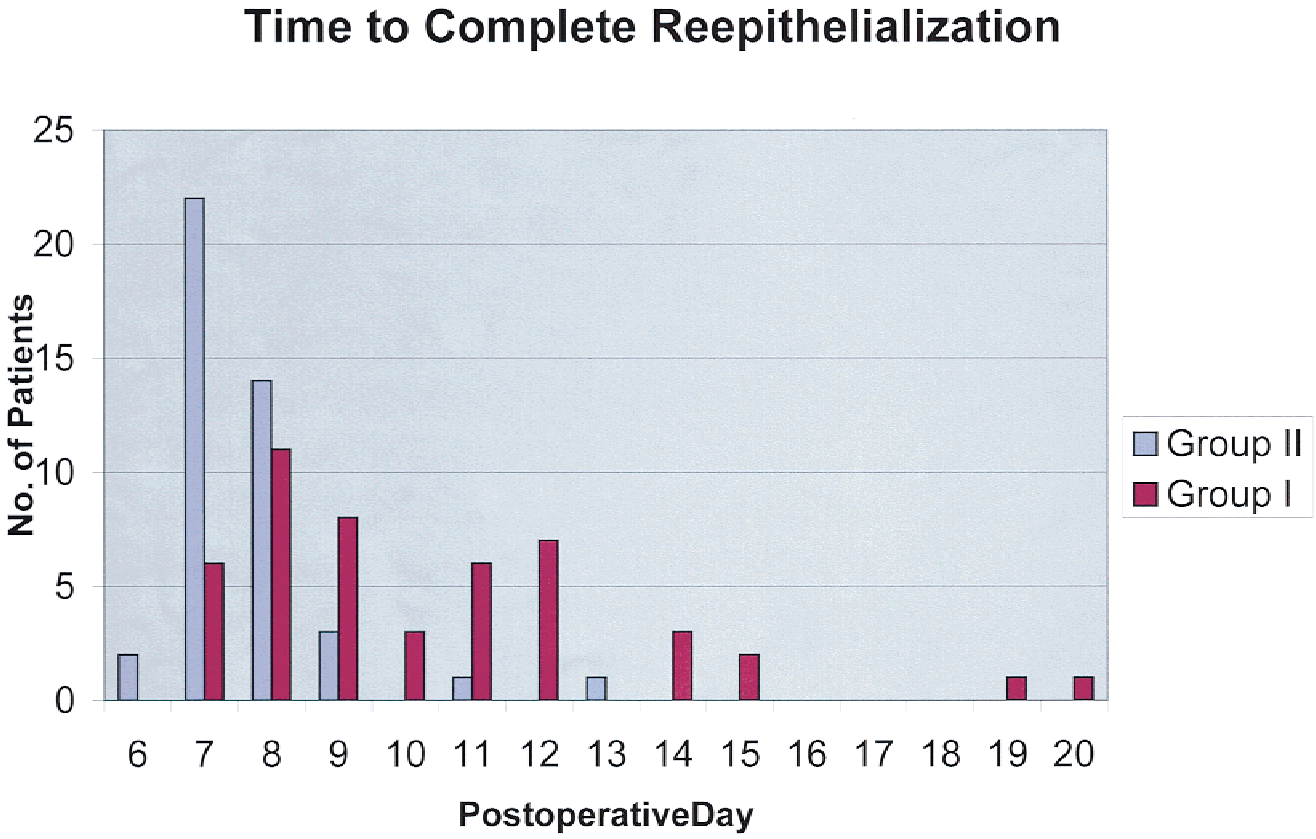

Fig. 1. Time to complete reepithelialization.

within the first week after laser resurfacing during the process of reepithelialization [5,6]. Infections with multiple organisms occured in more than 50% of cases, with *Candida* present in 25% of infections [5].

The issue of oral proplylactic antibiotics is complex, controversial, and unclear. Due to the cosmetic nature of resurfacing procedures, most patients are prescribed an oral proplylactic antibiotic and antiviral [5]. Antifungal treatment, however, is considered only in women with a previous history of oral, vaginal, or nail candidiasis.

In healthy patients, candidiasis is a minor self-limited disease amenable to topical treatment. In patients with full-face resurfacing, the intact skin surface, which serves as a vital barrier against infection, is compromised. Newly resurfaced skin is an open wound, exposing the upper dermis. The tissue effect immediately after laser resurfacing is similar to that of dermabrasion, deep chemical peel, or second-degree burn. As in a superficial burn, the newly resurfaced skin produces copious drainage, has mild to moderate crusting, and immediately becomes colonized with bacteria [8]. Local immunosuppression occurs with thermal injury, further predisposing the wound to bacterial, viral, and fungal infections [8]. Administration of prophylactic antibiotics may further predispose the open wound to low-grade colonization with *Candida*. Wound healing may then be retarded, thus increasing the potential for subsequent scarring, i.e., dyspigmentation, textural change, and prolonged erythema.

Our results indicate that the time to complete skin reepithelialization was shortened when treated with systemic fluconazole in addition to antibiotics. There could be two possible explanations for this. First, oral fluconazole acts as a fungistatic agent, curbing infection and colonization, thus leading to more rapid healing. Second, based on provocative studies by Zervos et al., it was suggested that fluconazole increases bactericidal activity of neutrophils in vitro [9,10]. It has been demonstrated that neutrophilic activity is enhanced by fluconazole [9,10]. Because the initial arrest of *Candida* is dependent on functional phagocytes, enhanced neutrophilic phagocytic activity can arrest both the yeast and bacterial in-

Fig. 2. Group I. **Top:** Preoperative. **Bottom:** Postoperative day 8, demonstrating incomplete reepithelialization with persistent oozing and crusting.

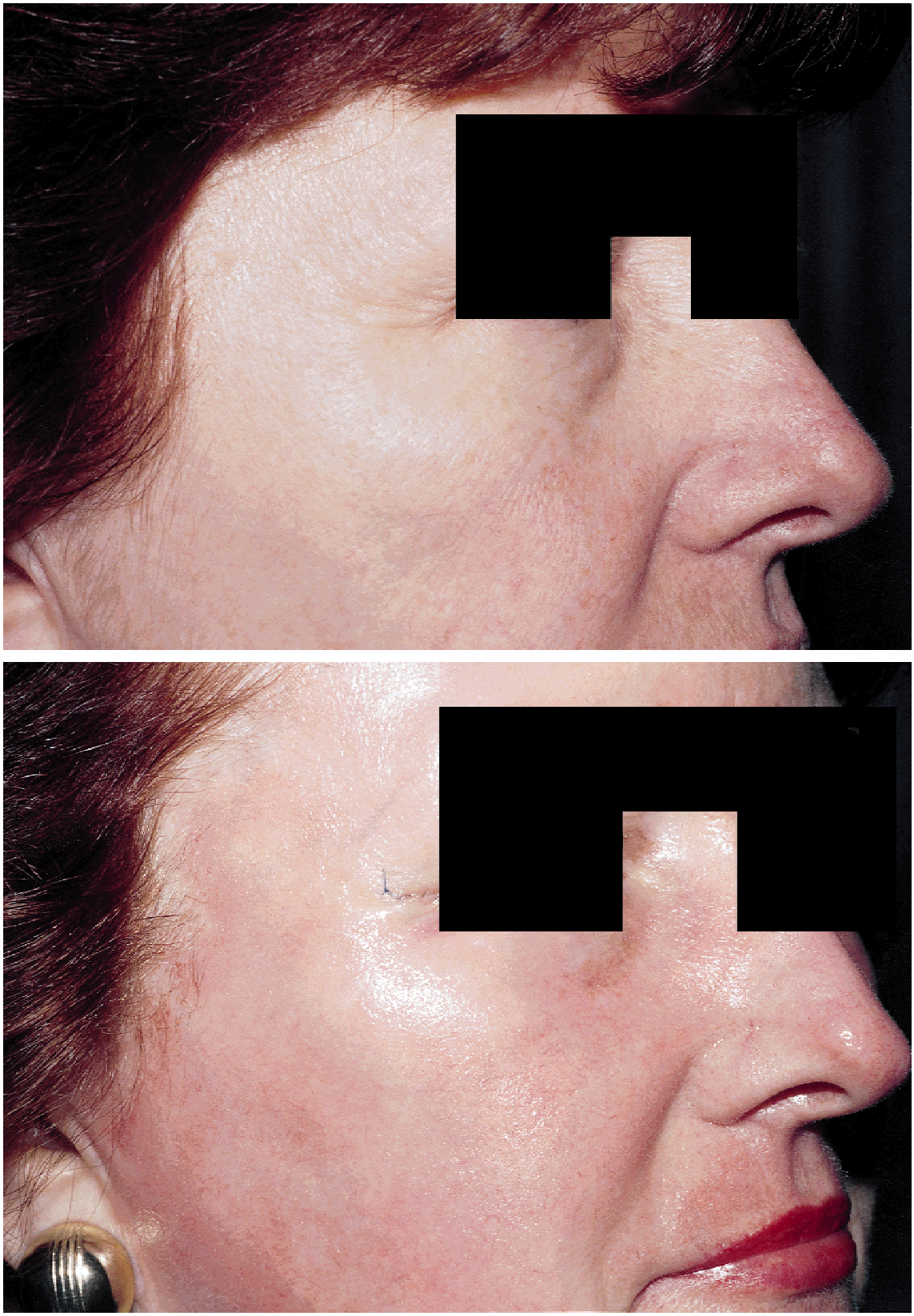

Fig. 3. Group II. **Top:** preoperative. **Bottom:** postoperative day 8, demonstrating complete reepithelialization. Erythema has begun to fade. Patient underwent four lid blepharoplasties. Sutures are still present in the upper eyelids.

fection. As pointed out earlier, most infections are mixed (bacterial and fungal); therefore, fluconazole may actually be effective in curbing both fungal and bacterial infections. Fluconazole appears to behave synergistically when given with cephalosporins or ciprofloxacin to promote reepithelialization.

The time to reepithelialization in patients within group I, who received cephalexin or ciprofloxacin alone, was also compared. Each group consisted of 24 patients. The group receiving cephalexin reepithelialized in 9.79 ± 2.61 days versus 10.75 ± 3.17 days for the group receiving ciprofloxacin. There was no statistical difference in healing time when comparing cephalexin with ciprofloxacin ($P < 0.134$). The choice of antibiotic does not appear to affect the rate of reepithelialization.

The rationale for considering prophylaxis with antifungal drugs is to decrease morbidity in patients at risk of infection. Laser resurfacing is an elective procedure, and any possibility of reducing the risk of scarring is significant. In the literature to date, fluconazole or other antifungal treatment is only used routinely for patients at risk for candidiasis. Manuskiatti et al. reported yeast infections in 1.8–2.2% of patients not receiving antifungal proplylaxis [6]. Their study encourages the use of antifungal prophylaxis but does not specify the conditions studied, i.e. the dosage, length of time the drug was used, and the number of patients using it as prophylaxis. We believe that our study is the first to document the effects on reepithelialization of routine prophylactic use of fluconazole in patients undergoing full-face laser resurfacing.

Fluconazole is a synthetic triazole derivative, is fungistatic, and acts by inhibiting fungal membrane sterol synthesis and preventing fungal cell replication. Fluconazole is much more selective for cytochrome P450 enzymes in fungi than mamallian cells. Fluconazole is poorly bound to plasma proteins (12%) and is widely distributed through body tissues and fluids including cerebrospinal fluid. It is eliminated mainly by renal rather than by hepatic mechanisms, in contrast to other systemic azole antifungals [11]. The drug does not have deleterious effects on the host immune response [11]. Synergy of human neutrophils with fluconazole in killing *Candida* species has been demonstrated in vitro by Brummer et al. [12]. Other limited literature also establishes immunoadjuvant properties of fluconazole [9,10,12–14].

Fluconazole is generally well tolerated, with a total incidence of adverse effects at 16% in patients receiving the drug for longer than 7 days. The manufacturer states that adverse effects have been reported more frequently in patients with HIV. Half of the adverse effects comprised of gastrointestinal complaints. Other complaints included headache (1.9%) and skin rashes (1.8%) [11]. Transient hepatic enzyme elevations occur in fewer than 5% of the general population receiving fluconazole but are higher in HIV patients. Evaluation of other adverse effects and establishment of causal relation to fluconazole has been difficult because the drug has been used in many patients on multiple medications with serious underlying diseases. Of note is a potentially serious drug interaction of cisapride and azole antifungals including fluconazole. Fluconazole inhibits the metabolism of cisapride. Elevated cisapride concentrations have been associated with QT prolongation, syncopal episodes, and cardiac dysrhythmias [15,16]. Other drugs that inhibit cisapride metabolism include erythromycin, troleandomycin, clarithromycin, and cimetidine [15,16].

It is concerning that widespread clinical use of fluconazole may influence the development of resistance or alter patterns of pathogen distribution. Resistance is most common in HIV patients with advanced disease and appears to be related to cumulative fluconazole dose [11,17]. For patients other than those with AIDS, there is less conclusive evidence for the presence of resistance [17]. The short-term use of fluconazole in healthy patients such as ours undergoing cosmetic procedures should not contribute toward the problem of resistance. Prophylaxis with antibiotics is a contentious subject, and more controlled studies are required for appropriate evaluation and conclusions.

CONCLUSION

In summary, patients undergoing full-face laser resurfacing may experience a prolonged exudative phase, crusting, pronounced erythema, and delayed wound healing. This study demonstrates that fluconazole administered postoperatively between days 3 and 8 significantly reduces the time to reepithelialization. Fluconazole should be considered prophylactically in addition to antibiotic and antiviral medications in patients undergoing full-face CO_2 laser resurfacing.

REFERENCES

1. Fitzpatrick RE. Laser resurfacing of rhytides. Dermatol Clin 1997;15:431–447.
2. Bernstein LJ, Kanvar AB, Grossman MC, Geronemus RG. The short- and long-term side effects of carbon dioxide laser resurfacing. Dermatol Surg 1997;23:519–525.
3. Nanni CA, Alster TS. Complications of carbon dioxide laser resurfacing. An evaluation of 500 patients. Dermatol Surg 1998;24:315–320.
4. Nanni CA, Alster TS. Complications of cutaneous laser surgery. A review. Dermatol Surg 1998;24:209–219.
5. Sriprachya-Anunt S, Fitzpatrick RE, Goldman MP, Smith SR. Infections complicating pulsed carbon dioxide laser resurfacing for photoaged facial skin. Dermatol Surg 1997;23:527–533.
6. Manuskiatti W, Fitzpatrick RE, Goldman MP, Krejci-Papa N. Prophylactic antibiotics in patients undergoing laser resurfacing of the skin. J Am Acad Dermatol 1999; 40:77–84.
7. Fulton JE. Complications of laser resurfacing—methods of prevention and management. Dermatol Surg 1997;24: 209–219.
8. Duke D, Grevelink JM. Care before and after laser skin resurfacing. Dermatol Surg 1998;24:201–206.
9. Zervos EE, Bass SS, Robson MC, Rosemurgy AS. Fluconazole increases bactericidal activity of neutrophils through non-cytokine-mediated pathway. J Trauma Injury Infect Crit Care 1996;41:465–470.
10. Zervos EE, Bass SS, Robson MC, Rosemurgy AS. Fluconazole increases bactericidal activity of neutrophils. J Trauma Injury Infect Crit Care 1996;41:10–14.
11. Goa KL, Barradell LB. Fluconazole. An update of its pharmacodynamic and pharmacokinetic properties and therapeutic use in major superficial and systemic mycoses in immunocompromised patients. Drugs 1995;50: 658–690.
12. Brummer E, Stevens DA. Synergy of human neutrophils with fluconazole in killing Candida species. Mycopathologia 1996;134:115–120.
13. Natarajan U, Randhawa N, Brummer E, Stevens DA. Effect of granulocyte-macrophage colony-stimulating factor on candidacidal activity of neutrophils, monocytes or monocyte-derived macrophages and synergy with fluconazole. J Med Microbiol 1998;47:359–363.
14. DiFrancesco P, Gaziano R, Casalinuovo IA, Palamara AT, Favalli C, Garaci E. Antifungal and immunoadjuvant properties of fluconazole in mice immunosuppressed with morphine. Chemotherapy 1997;43:198–203.
15. Bedford TA, Rowbotham DJ. Cisapride. Drug interactions of clinical significance. Drug Safe 1996;15:167–175.
16. Gray VS. Syncopal episodes associated with cisapride and concurrent drugs. Ann Pharmacother 1998;32:648–651.
17. Rex JH, Rinaldi MG, Pfaller MA. Resistance of Candida species to fluconazole. Antimicr Agents Chemother 1995; 39:1–8.